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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/002,634

12/05/2001

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033136-226

1971

7590

02/25/2005

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EXAMINER

BELYAVSKYI, MICHAEL A

ART UNIT

PAPER NUMBER

1644

DATE MAILED: 02/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action
Before the Filing of an Appeal Brief**

Application No.

10/002,634

Applicant(s)

BOLTON ET AL.

Examiner

Michail A Belyavskyi

Art Unit

1644

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 18 January 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The reply was filed after the date of filing a Notice of Appeal, but prior to the date of filing an appeal brief. The Notice of Appeal was filed on 18 January 2005. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
- (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ They raise the issue of new matter (see NOTE below);
- (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
- The status of the claim(s) is (or will be) as follows:
- Claim(s) allowed: ____.
- Claim(s) objected to: ____.
- Claim(s) rejected: 12-18.
- Claim(s) withdrawn from consideration: ____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 11. does NOT place the application in condition for allowance because:

1. Claims 12-18 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of decreasing the expression of one or more of the inflammatory cytokines IFN-g and IL-6 from cells in mammalian patients comprising administering to the patient an effective amount of stressed mammalian blood cells wherein said blood cells have been extracorporeally subjected to both oxidative conditions and UV radiation does not reasonably provide enablement for a method for treatment or prophylaxis chronic fatigue syndrome in a patient comprising administering to the patient an effective amount of stressed mammalian blood cells wherein said blood cells have been extracorporeally subjected to both oxidative conditions and UV radiation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action, mailed on 08/26/04.

Applicant's arguments, filed 1/18/05 have been fully considered, but have not been found convincing.

Applicant asserts that: (i) method of prevention, as well as treatment are enabled by the specification, the methodology for treatment is the same as that for prophylaxis and there no basis for distinguishing between treatment and prophylaxis.

Contrary to Applicant's assertion, it is the Examiner position that specification does not reasonably provide enablement for a method for treatment or prophylaxis of any inflammatory disease, including chronic fatigue syndrome in a patient comprising administering to the patient an effective amount of stressed mammalian blood cells wherein said blood cells have been extracorporeally subjected to both oxidative conditions and UV radiation.

Moreover, as was stated in the previous Office Action, since there is no animal model studies and data in the specification to show the effectively of treatment or prophylaxis of chronic fatigue syndrome in a patient comprising administering to the patient an effective amount of stressed mammalian blood cells wherein said blood cells have been extracorporeally subjected to both oxidative conditions and UV radiation it is unpredictable how to correlate a contact hypersensitivity (CHS) test on Balb/c mice and the decrease in the expression levels for cytokines IFN-g and IL-6 in the lymph tissue of the treated animals with claimed in vivo use. Applicant himself acknowledge that etiology of CFS remains unknown and it is well known in the art that excessive sensitivity to IL-6 are almost certainly not the only factor controlling CFS (see page 9, lines 20-25 in particular)

Moreover, the Examiner disagree with Applicant's statement that "there no basis for distinguishing between treatment and prophylaxis"

The nature of the invention is such that it would require the administration of blood cells that have been extracorporeally subjected to both oxidative conditions and UV radiation that would prevent a mammalian subject from having inflammatory disease. The burden of enabling the prevention of a disease (i. e. the need for additional testing) would be greater than that of enabling a treatment due to the need to screen those humans susceptible to such diseases and the difficulty of proof that the administration of stressed blood cells was the agent that acted to prevent the condition. Further, the specification does not provide guidance as to how one skilled in the art would go about screening those patients susceptible to any inflammatory disease, including chronic fatigue syndrome within the scope of the presently claimed invention. Nor is guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed compounds in preventing these disease states. Accordingly, undue experimentation is necessary to determine screening and testing protocols to demonstrate the efficacy of the presently claimed invention.

2. Claim 12-18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/07463 or U.S. Patent No. 5,980,954 or WO00/06703 each in view of CDC Report (1999) set forth in the previous Office Action, mailed on 08/26/04.

Applicant's arguments, filed 1/18/05 have been fully considered, but have not been found convincing.

Applicant asserts that : one skilled in the art would not be motivated to combine the cited references

Contrary to Applicant's assertion, as was stated in the previous Office Action, The WO ' 703 teaches a method of treating GVHD in a mammalian patient comprises administering to the patient stressed mammalian blood cells (see the entire document Abstract in particular . The WO '703 teaches that stress blood cells have been extracting from the patient an aliquot of blood of volume, contacting the aliquot of blood, extracorporeally subject to at both oxidative conditions, ultraviolet radiation and heat stress simultaneously. (see overlapping pages 5-6 and 7 in particular). The WO '703 teaches that oxidative environment, such as a mixture of ozone, wherein an ozone content from about 1 to about 100 mg/ml and oxygen bubbled through the blood aliquot, from about 0.5 to 60 min (pages 7 and 9 , in particular). The WO '703 teaches that the temperature stressor is in a range from about 40 to about 55o C (see pages 8 and 11 in particular). The WO '703 teaches that UV stressor is UV-c radiation (see page 8 in particular). Wherein the patient is human and the aliquot of modified mammalian blood is the patient's own blood , of volume from about 0.1- 500 ml (page 7, in particular).

The WO ' 436 teaches a method of treating an inflammatory disease including inflammatory bowel disease and rheumatoid arthritis in a mammalian patient comprises administering to the patient stressed mammalian blood cells (see the entire document, pages 1, 17, and 23 in particular) . The WO ' 436 teaches that stress blood cells have been extracting from the patient an aliquot of blood of volume, contacting the aliquot of blood, extracorporeally subject to at both oxidative conditions, ultraviolet radiation and heat stress simultaneously. (see overlapping pages 13-14 and 16-17 in particular). The WO ' 436 teaches that oxidative environment, such as a mixture of ozone, wherein an ozone content from about 1.0 to about 100 mg/ml and oxygen bubbled through the blood aliquot, from about 0.5 to 60 min (pages 14-15, in particular). The WO ' 436 teaches that the temperature stressor is in a range from about 40 to about

55o C (see page 14 in particular). The WO ' 436 teaches that UV stessor is UV-c radiation (see page 15 in particular). Wherein the patient is human (page 8, paragraph 3 in particular), and the aliquot of modified mammalian blood is the patient's own blood (page 12, paragraph 4 in particular), of volume from about 0.01-400 ml (pages 8, 13, in particular).

The US Patent '954 teaches a method of treating an inflammatory disease including inflammatory bowel disease and rheumatoid arthritis in a mammalian patient comprises administering to the patient stressed mammalian blood cells (see the entire document, column 1, and overlapping columns 7 -8 in particular). The US Patent '954 teaches that stress blood cells have been extracting from the patient an aliquot of blood of volume, contacting the aliquot of blood, extracorporeally subject to at both oxidative conditions, ultraviolet radiation and heat stress simultaneously. (see column 6, in particular). The US Patent '954 teaches that oxidative environment, such as a mixture of ozone, wherein an ozone content from about 0.5 to about 100 mg/ml and oxygen bubbled through the blood aliquot, from about 0.5 to 60 min (see overlapping columns 7-8 and Claim 5 in particular). US Patent '954 teaches that the temperature stressor is in a range from about 40 to about 55o C (see column 7 and claim 4 in particular). The US Patent '954 teaches that UV stessor is UV-c radiation (see column 8 in particular). Wherein the patient is human, and the aliquot of modified mammalian blood is the patient's own blood of volume from about 0.01-400 ml (column 9 and claim 2 in particular).

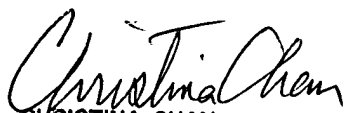
It is noted that that the above references are silent about the fact that disease condition in a patient is mediated by excess inflammatory cytokine production and or abnormal sensitivity of the patient to one or more inflammaroty cytokine, i.e. IL-6 . However, it is clear that both the prior art references and applicant administered the same composition, i.e. stressed mammalian blood cells to the same patient to achieve the same results, i.e. treating disease. Even though applicant has proposed the mechanism by which stressed mammalian blood cells alleviates symptoms of an CFS this does not appear to distinguish the prior art teaching the same methods to achieve the same end result. Mere recognition of latent properties in the prior art does not render known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. If the prior art structure is capable of performing the intended use i.e. to treat CFS, then it meets the claim.

WO 98/07463 , U.S. Patent No. 5,980,954 or WO00/06703 do not teach treating chronic fatigue syndrome.

CDC Report teaches that chronic fatigue syndrome is an inflammatory disease mediated by excess inflammatory cytokine production.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of CDS Report to those of WO 98/07463 or U.S. Patent No. 5,980,954 or WO00/06703 to obtain a claimed method for treating CFS.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because chronic fatigue syndrome is an inflammatory disease mediated by excess inflammatory cytokine production as taught by CDC Report and can be treated by the method for treatment of an inflammatory diseases taught by WO 98/07463 , U.S. Patent No. 5,980,954 or WO00/06703. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.


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